

Applicants submit that the specification has provided ample data on the interaction between Smad6 and Hoxc-8, demonstrating clearly that Applicants had possession of the claimed invention at the time the application was filed. The interaction between Smad6 and Hoxc-8 was identified in a yeast two-hybrid approach, and further demonstrated by co-immunoprecipitation assays in cells. Gel shift assays show that Hoxc-8 interacts with Smad6 as a heterodimer when binding to DNA. More importantly, the Smad6/Hoxc-8 complex inhibited both Smad1 interaction with Hoxc-8 in gel shift assays and transcription activity mediated by Smad1.

Figure 1 shows the specific interaction of Smad6 with Hoxc-8 in a yeast two-hybrid system. Figure 2 shows the interaction of Smad1 with Hoxc-8 *in vivo*. Figure 3A shows the complex of Smad6 and Hoxc-8 blocks the interaction of Smad1 with Hoxc-8. Figure 3B shows the complex of Smad6 and Hoxc-8 blocks the interaction of Smad4 with Hoxc-8. Figure 4B shows that Smad6 and Hoxc-8 inhibit Smad1B-induced transcription. Therefore, in view of the experimental data provided in Applicants' specification, a person having ordinary skill in the art would readily recognize that

Applicants had possession of Smad6 and Hoxc-8 of the claimed method at the time the application was filed.

The Examiner contends that the specification does not provide any sequences for Smad6 or Hoxc-8 such that the skilled artisan would recognize the structural features of proteins encompassed in the terms Smad6 and Hoxc-8. Applicants respectfully disagree.

Applicants submit that the practice of the claimed methods of the present invention does not require knowledge about the structural features of Smad6 and Hoxc-8. The present invention only requires cloning Smad6 and Hoxc-8 into suitable vectors. Smad6 and Hoxc-8 are well known in the art and one of ordinary skill in the art can readily obtain published sequences for these proteins in the prior art and clone these proteins according to standard genetic engineering procedures. For these reasons, Applicants submit that the specification has provided sufficient written description for Smad6 and Hoxc-8. The Examiner has not provided any scientific evidence to the contrary. Accordingly, Applicants respectfully request that the rejection of claims 11-14 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 11-14 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is respectfully traversed.

The Examiner contends that it is unclear what proteins would be encompassed in the terms "Smad6" and "Hoxc-8". The Examiner further contends that it is unclear because the same proteins may be referred to in the prior art by an alternative name. Applicants respectfully disagree.

Applicants submit that Smad6 and Hoxc-8 proteins are well known in the art and one of ordinary skill in the art would readily recognize what these proteins are based on description and sequences readily available and published in the prior art. As described in the specification, Smads mediate signaling of the superfamily of transforming growth factor- $\beta$  (TGF- $\beta$ ). Smad6 and Smad7, a subgroup of Smad proteins, antagonize the TGF- $\beta$  signals. These two Smads, induced by TGF- $\beta$  or bone morphogenetic protein (BMP), form stable association with activated type I receptors, which, in turn, block phosphorylation of ligand-induced Smads.

In vertebrates, there are 39 Hox homeobox-containing transcription factor genes, organized into four separate chromosome

clusters, which play critical roles in the process and patterning of vertebrate embryonic development. These 39 genes are subdivided into 13 paralogous groups on the basis of duplication of an ancestral homeobox cluster during evolution, sequence similarity and position within the cluster. Each paralog group has been demonstrated to be responsible for morphogenesis of a particular embryonic domain or structure. There are three members in Hox paralog group VIII, Hoxb-8, Hoxc-8 and Hoxd-8. Northern blot analysis shows that Hoxc-8 is expressed during human embryo development at high levels in spinal cord, backbone and limbs and at a lower level in heart.

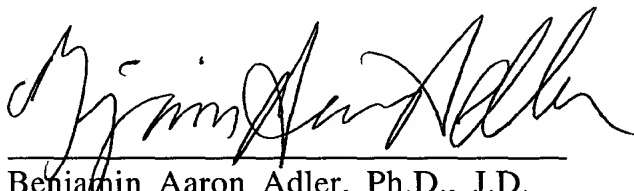
As shown in the above discussion, Smad6 and Hoxc-8 are well known and have been extensively studied in the prior art. Applicants further submit that one of ordinary skill in the art would not be confused by the purported situation of naming the same proteins with different names because Smad6 and Hoxc-8 proteins have been well characterized. Moreover, the Examiner has not provided any scientific evidence showing the Smad6 and Hoxc-8 proteins are named differently in the prior art. Hence, Applicants submit that the Smad6 and Hoxc-8 proteins have been adequately described in the present application. Accordingly, Applicants

respectfully request that the rejection of claims 11-14 under 35 U.S.C. §112, second paragraph, be withdrawn.

This is intended to be a complete response to the Office Action mailed September 11, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Oct 28, 2002



Benjamin Aaron Adler, Ph.D., J.D.  
Registration No. 35,423  
Counsel for Applicant

ADLER & ASSOCIATES  
8011 Candle Lane  
Houston, Texas 77071  
(713) 270-5391 (tel.)  
(713) 270-5361 (facs.)  
badler1@houston.rr.com